A NEW PARADIGM FOR THE TREATMENT OF OSTEOARTHRITIS

Invossa™ Genetically Modified Cell Therapy
Company Profile

Company Overview
Developing innovative regenerative therapies
Lead product for orthopedic indications
Based on proprietary allogeneic cell therapy technology

Products
Novel biologics for cartilage, disc and nerve repair
Commercial-scale production and low COGs
Blockbuster market potential
# Robust Product Pipeline

Allogeneic cell therapy products developed to repair tissue

<table>
<thead>
<tr>
<th>Products</th>
<th>R&amp;D</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invossa™</strong></td>
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<tr>
<td>Cartilage regeneration</td>
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<tr>
<td>Knee osteoarthritis</td>
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<tr>
<td>Hip osteoarthritis (planned)</td>
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<tr>
<td><strong>TG-D</strong></td>
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<tr>
<td>Disc regeneration</td>
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<tr>
<td>Degenerative disc disease</td>
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<td><strong>TG-N</strong></td>
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<tr>
<td>Nerve regeneration</td>
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<tr>
<td>Spinal cord injury</td>
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</table>
**Invossa™: The Technology**

Allogeneic cell therapy to repair cartilage in osteoarthritis

<table>
<thead>
<tr>
<th>Platform</th>
<th>Allogeneic cell therapy</th>
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<tbody>
<tr>
<td>Purpose</td>
<td>Cartilage regeneration</td>
</tr>
<tr>
<td>Indication</td>
<td>Knee osteoarthritis (OA)</td>
</tr>
<tr>
<td>Cell Type</td>
<td>Human chondrocytes expressing TGFβ-1</td>
</tr>
<tr>
<td>Stage</td>
<td>Initiating Phase 3</td>
</tr>
</tbody>
</table>

![Diagram showing the process of allogeneic cell therapy to repair cartilage in osteoarthritis](https://example.com/slide.png)
The Promise of Cell Therapy

To repair, replace, and restore functional living tissue

**Autologous**

- Autologous cells are harvested from an individual patient, expanded over many weeks, then returned to the same patient.
- Expensive
- High COGS
- Not Easily Scalable
- Autologous = Patient Specific
- Two Surgeries Required
- Potential Complications (Adhesions, Hypertrophy)

**Allogeneic**

- Allogeneic cells are expanded cells originating from a single universal donor to provide treatment to a large patient population.
- Inexpensive
- Low COGS
- Easily Scalable
- Allogeneic = Universal Donor
- No Surgery Required

**Commercial Disadvantages**

**Commercial Advantages**
Osteoarthritis: A Debilitating Disease
Symptoms include severe pain, swelling & stiffness
Market Opportunity

- ~6.6M OA of the knee patients are under active management
  - Treatment progresses from NSAIDS to injections, then surgery
  - Significant treatment gap prior to surgery

- Physicians cite the need for additional options for moderate to severe patients
Invossa™ Clinical Development
Invossa™ Phase I Clinical Study Synopsis
A Randomized, Double-blind, Dose Escalation Study

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose</th>
<th># Patients</th>
</tr>
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<tbody>
<tr>
<td>G1</td>
<td>TG-C (3.0 x 10^6 cells/knee)</td>
<td>4</td>
</tr>
<tr>
<td>G2</td>
<td>TG-C (1.0 x 10^7 cells/knee)</td>
<td>4</td>
</tr>
<tr>
<td>G3</td>
<td>TG-C (3.0 x 10^7 cells/knee)</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Objectives:** Safety, dose response & distribution
- **Patient population:** K&L confirmed OA patients scheduled for surgery
- **Duration of observation:** 12 months
- **Demographics**
  - Gender: Male (n=2), Female (n=10)
  - Age: 60.5 years old; BMI: 34.8 kg/m²
- **Sites:** 2 Sites
Invossa™ Phase I Clinical Study Summary

• 1 year follow-up completed with no safety concerns
  • Safe and well-tolerated at all dose levels tested
  • No treatment related SAEs (Severe Adverse Events)
• Safety measurements
  • TGF-β1 level within normal range
  • No detection of vector DNA or RCR
# Phase 2 Study Design for Invossa™

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Multi-center, double-blinded randomized, placebo-controlled*</th>
</tr>
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<tbody>
<tr>
<td>Study Group</td>
<td>100 randomized patients, ages 18-70 knee osteoarthritis (Grade 3)</td>
</tr>
<tr>
<td>Treatment Arms</td>
<td>Invossa™: 3x10^7 cells/joint (N=67) Control: single saline injection (N=33)</td>
</tr>
<tr>
<td>Efficacy Endpoints</td>
<td>Knee pain &amp; functionality Cartilage regeneration (MRIs)</td>
</tr>
</tbody>
</table>

*Study designed to see at least a 25% difference from control (alpha=0.05, 80% power)
U.S. Phase 2 Results for Invossa™
Primary efficacy data analysis completed with 12-month follow-up

Visual Analog Scale (VAS) Pain Index
- From 0 (no pain) to 100 (extreme pain)
- Decrease in score = decrease in pain

IKDC Subjective Knee Form (function)
- Patient-oriented, knee-specific questionnaire
- Assess knee symptom, activity & function
- From 0 to 100, higher score = improvement

Evaluation Schedule
- At screening, baseline, 24-hr post-dosing
- At 1, 3, 6, 12, 18 & 24 Months
- Primary efficacy analysis at 1-yr period
U.S. Phase 2 MRI Results for Invossa™

MRI data shows filling of cartilage defect in Invossa™ treated patients

Schedule
0, 3, 6, 12 months

Structure
Bone (black), healthy cartilage (grey)
Damaged cartilage & joint fluid (white)

Appearance

Scoring Systems
MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue)
WORMS (Whole-Organ Magnetic Resonance Imaging Score)
Safety

- The most common AEs definitely related to treatment with Invossa™ were joint inflammation, arthralgia and joint effusion.
- Four SAEs were experienced, two in the Invossa™ group and two in the placebo group.
- These SAEs were not considered to be related to the study medication.
Phase 2 Trial Summary

Invossa™ has been shown to improve pain and function in the knee joint, and to delay disease progression by reducing the rate of joint space narrowing in patients with primary osteoarthritis of the knee.
### Invossa™ Clinical Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>PHASE 2 COMPLETED</td>
<td>OCT 2014</td>
</tr>
<tr>
<td>END-OF-PHASE 2 FDA MEETING</td>
<td>4Q 2014</td>
</tr>
<tr>
<td>SPA AGREEMENT WITH FDA</td>
<td>MAY 2015</td>
</tr>
<tr>
<td>TREAT FIRST PATIENT</td>
<td>1H 2016</td>
</tr>
<tr>
<td>COMPLETE PHASE 3 Q1</td>
<td>2018</td>
</tr>
</tbody>
</table>
Phase 3 Study Design

Two Identical Protocols

• Randomized double-blind, placebo-controlled, multi-center studies in subjects with Kellgren & Lawrence grade 2 or 3 OA of the knee
  • 510 subjects in each study (340 active, 170 placebo)
• First study to be conducted exclusively in the U.S.; second to include EU

• Co-primary endpoints
  • Knee function as measured by the WOMAC (Western Ontario & McMaster Universities)
  • Osteoarthritis index and pain as measured by VAS (Visual Analog Scale)

• Secondary endpoints include
  • Delay in disease progression as measured by joint space width based on radiography
Dramatic Market Opportunity
Minimally-invasive disease-modifying therapies for OA currently unavailable

Pain Relievers

- Oral & Topical Meds
  - Acetaminophen (Tylenol)
  - NSAIDS (ibuprofen, naproxen)
  - COX-2 inhibitors (Celebrex)

- Injections
  - Corticosteroids
  - Hyaluronic acids (Synvisc-One™)

Surgery

- Arthroscopy
- Knee replacement
- Bone marrow stimulation
- Realigning bones (osteotomy)

Less Invasive

Treatment Gap

More Invasive
Invossa Competitive Advantage
Offers a minimally-invasive disease-modifying treatment for osteoarthritis

**Effective**
- Regenerates cartilage
- Reduces knee pain
- Improves mobility

**Minimally-Invasive**
- Non-surgical
- Simple & convenient
- Effective & affordable

**Mass Producible**
- Off-the-shelf product
- Optimized for scale-up
- 1.5M doses per donor

**Market Potential**
- Untapped global market
- Large aging population
- Significant market growth
Dramatic Market Opportunity  
Minimally-invasive disease-modifying therapy coming soon

**Pain Relievers**

- Oral & Topical Meds
  - Acetaminophen (Tylenol)
  - NSAIDS (ibuprofen, naproxen)
  - COX-2 inhibitors (Celebrex)

- Injections
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  - Hyaluronic acids (Synvisc-One™)

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**Treatment Gap**

**Invossa™**

~$2B Opportunity*

- First and only genetically-modified cell therapy injectable for OA pain and cartilage regeneration

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**Surgery**

- Arthroscopy ⇒ Knee replacement
- Bone marrow stimulation
- Realigning bones (osteotomy)

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*LEK Survey 2015
## Overview

<table>
<thead>
<tr>
<th>Location</th>
<th>Rockville, Maryland, USA</th>
</tr>
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</table>
| Major Shareholders | Kolon group 69.2%  
                     | Individuals 30.8%       |

## Key Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1999</td>
<td>TissueGene, Inc. established</td>
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<tr>
<td>2001</td>
<td>Acquisition of key technology patents for TG-C in US</td>
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<tr>
<td>2005</td>
<td>Selected as a “Biostar Project” sponsored by the government of Korea</td>
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<td>(funding of $5.2M)</td>
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<tr>
<td>2006~2014</td>
<td>TG-C phase 1,2 clinical</td>
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<tr>
<td>2015</td>
<td>TG-C phase 3 clinical trials in planning</td>
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Value Proposition

• Exploring strategic partnerships for lead program

• Seeking strategic investment as we initiate phase 3 trials

• Initiating development of additional product candidates & planning portfolio expansion

• Robust patent portfolio with U.S. expiry in 2031
Thank you.

TissueGene
DEVELOPING REGENERATIVE THERAPIES FOR ORTHOPEDIC DISEASES
To improve the quality of life for patients worldwide...

www.TissueGene.com
Bob Newman, COO
rnewman@tissuegene.com
(301) 921-6000, x135